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Effect of Regional Ischemia on the Left Ventricular End-Systolic Pressure-Volume Relation in Chronically Instrumented Dogs

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The slope of the left ventricular end-systolic pressure-volume relation has been proposed as a sensitive index of left ventricular function since it increases in response to positive inotropic agents and decreases with global depression of contractility. The effect of a segmental depression of left ventricular contractile function produced by circumflex coronary artery occlusion on the left ventricular end-systolic pressure-volume relation was evaluated in seven chronically instrumented dogs. Left ventricular volume was calculated from three ultrasonically measured, orthogonal left ventricular endocardial dimensions. Left ventricular pressure was measured with a micromanometer. The left ventricular end-systolic pressure-volume relation was generated by occlusion of the inferior vena cava, before and after inducing regional ischemia, in the presence of autonomic blockade with propranolol and atropine.

The end-systolic data in each dog, before and after coronary occlusion, were fit to the equation, $P = E(V - V_0)$, with $r \geq 0.95$ in all cases. Coronary occlusion shifted the left ventricular end-systolic pressure-volume relation to the right in each animal. During regional ischemia, the volume intercept (V_0) increased from 10.1 ± 7.8 to 20.4 ± 9.8 ml (mean ± SD) ($p < 0.005$). The slope (E) of the left ventricular end-systolic pressure-volume relation was relatively unchanged.

It is concluded that in intact dogs, regional left ventricular ischemia resulting from coronary occlusion produces a rightward shift of the left ventricular end-systolic pressure-volume relation. These results, which are consistent with previous studies of isolated nonejecting hearts, suggest that the volume intercept of the left ventricular end-systolic pressure-volume relation may be a more sensitive index of alterations in regional systolic function than the slope.

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The left ventricular end-systolic pressure-volume relation has been proposed as a measure of ventricular contractile function that is independent of loading conditions (1–4). The left ventricular end-systolic pressure is linearly related to the end-systolic volume in isolated hearts (1–3), chronically instrumented dogs (5) and human patients (6,7). Thus, the end-systolic pressure-volume relation can be described by its slope and the volume intercept at zero pressure. Changes in global contractile function alter the slope of the relation without affecting the volume intercept (1–5,8–11). Augmentation of contractile function increases the slope of the relation, while a decrease in contractility produced by global ischemia depresses the slope without altering the volume intercept. Sunagawa et al. (12) recently demonstrated a different response to segmental depression of left ventricular contractile function produced by coronary occlusion in the isolated nonejecting canine heart. Regional ischemia in this model produced a parallel rightward shift of the end-systolic pressure-volume relation (an increase in the volume intercept without a change in the slope) in the physiologic range. The effect of regional ischemia on the left ventricular end-systolic pressure-volume relation in the intact heart ejecting into the normal circulation has not been determined (12). Accordingly, this study was undertaken to investigate the effect of regional ischemia on the end-systolic pressure-volume relation of the ejecting left ventricle in chronically instrumented dogs.

Methods

Instrumentation. Seven healthy adult mongrel dogs were instrumented using halothane (1 to 2%) anesthesia after infusion of xylene (1 mg/kg) and sodium thiopental (6 mg/kg) (5,14). A left lateral thoracotomy was performed using ster-

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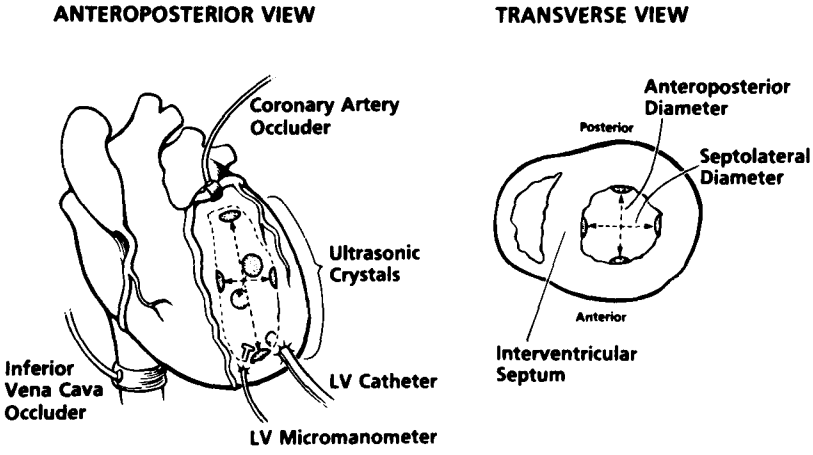

Figure 1. Diagrammatic representation of the instrumentation. LV = left ventricular.

ile techniques, and the pericardium was widely opened. A solid state micromanometer pressure transducer (Konigsberg Instruments) and a polyvinyl catheter (1.1 mm inner diameter) for transducer calibration were inserted through a left ventricular apical stab wound (Fig. 1). A small polyvinyl catheter was inserted into the left atrium for subsequent administration of drugs. Three pairs of ultrasonic crystals (5 MHz) were implanted in the endocardium of the left ventricle to measure the anterior to posterior, septal to lateral and base to apex (long axis) dimensions of the left ventricle (5,13). Inflatable hydraulic occluder cuffs were placed around the inferior vena cava and the proximal left circumflex coronary artery in seven dogs. In one animal (Dog 7), another occluder cuff was placed around the distal left anterior descending coronary artery after the origin of a large diagonal branch. The wires and tubing were tunneled subcutaneously and brought out through the skin of the neck.

Data collection. After full recovery from the thoracotomy (10 days to 2 weeks), the dogs were studied lying on their right side in a sling after sedation with intravenous fentanyl (0.02 to 0.04 mg/kg) in combination with droperidol (1.0 to 2.0 mg/kg) and intubation. Autonomic blockade was produced by the intravenous administration of atropine sulfate (0.2 mg/kg) and propranolol (2 mg/kg).

The left ventricular catheter was connected to a Statham P23Db pressure transducer and calibrated with a mercury manometer. The zero reference point was the vertebral column. The left ventricular pressure signal from the micromanometer was adjusted to match the fluid-filled catheter. The transit time of 5 MHz sound between the crystal pairs was determined and converted to distance, assuming a constant velocity of sound in blood of 1.55 m/ms. The first derivative of left ventricular pressure (dP/dt) was obtained electronically from the micromanometer signal using a resistance-capacitance circuit with a linear frequency response to 70 Hz. The signals were recorded on an eight channel oscillograph (Beckman Instruments). Analog signals were digitized using an on-line analog to digital converter (Dual Control Systems) at 10 ms intervals (100 Hz) and stored on a floppy disk memory system using a dedicated laboratory computer system (Zobex).

Experimental protocol. To minimize fluctuations in intrathoracic pressure, data were recorded during 12 second periods while the dogs were apneic after 15 seconds of hyperventilation (14). During the recording period, the endotrachial tube was opened to the atmosphere and the dogs were watched to be certain that they made no respiratory efforts.

Data were initially recorded during a steady state period to obtain baseline values. The control end-systolic pressure-volume relation was then generated by transient inferior vena cava occlusions (Fig. 2) (5). The left circumflex coronary artery was then occluded. After 2 minutes of occlusion, signals were recorded to obtain the hemodynamic values, which were used to document the production of ischemia (see Results). Then, the end-systolic pressure-volume relation was again generated by transient vena caval occlusions.

In one animal (Dog 7), the end-systolic pressure-volume relation was generated after occlusion of the distal left anterior descending coronary artery, the proximal left circumflex coronary artery and both the left circumflex and distal anterior descending coronary arteries.

Postmortem studies. At the conclusion of the experiments, the dogs were killed and the hearts examined to confirm the proper positioning of the instrumentation.

Data analysis. The stored digitized data were analyzed using a computer algorithm. Hemodynamic values in each dog were obtained by averaging the data obtained during the 12 second baseline recording periods. The data obtained during the vena caval occlusions were analyzed at end-systole. End-systole was defined as the time at which the ratio of left ventricular pressure to volume became maximal (3). End-diastole was defined as the Z point of the high fidelity left ventricular pressure tracing.

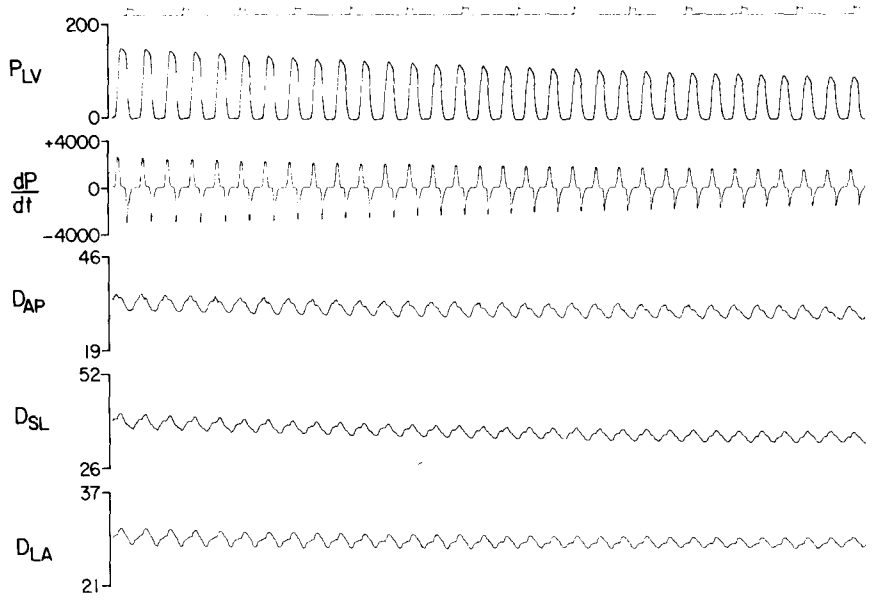

Figure 2. Representative control recording after occlusion of the inferior vena cava. The left ventricular pressure (P_{LV}) and the three left ventricular dimensions (D_{AP} = anteroposterior, D_{SL} = septal-lateral, D_{LA} = base to apex or long axis) progressively decrease, allowing determination of the left ventricular end-systolic pressure-volume relations. dP/dt = the first derivative of left ventricular pressure. The marks on the top are at 1 second intervals.

Left ventricular volume was calculated from the three endocardial left ventricular dimensions using the equation:

$$V = (\pi/6)D_{AP}D_{SL}D_{LA},$$

where D_{AP} = anteroposterior left ventricular dimension, D_{SL} = septal to lateral left ventricular dimension and D_{LA} = long-axis left ventricular dimension.

The end-systolic pressure and volume were fit by linear least squares analysis to the following equation:

$$P = E(V - V_0),$$

where P = left ventricular pressure, E = the slope of the end-systolic pressure-volume relation, V = left ventricular end-systolic volume and V_0 = the volume intercept of the end-systolic pressure-volume relation.

Left ventricular volume calculation. Left ventricular volume was calculated from three ultrasonically determined left ventricular dimensions. Although this method is similar to that used and validated by others (15,16), we determined endocardial dimensions directly and, thus, subtraction of left ventricular wall thickness or wall volume was not necessary. We have previously observed (5,14) that during vena caval occlusion, the stroke volume calculated as the difference between ultrasonically determined end-diastolic and end-ejection volumes is linearly related to the stroke volume simultaneously measured by ascending aortic flow probe ($r \geq 0.97$, SEE $\leq$ 1.0 ml). Because the regional ischemia produced in this study may have altered left ventricular geometry, we further evaluated our method of volume calculation in a dog that was additionally instrumented with an electromagnetic flow probe (Zepeda Instruments) in the ascending aorta. Crystal-derived and measured stroke volumes were compared during vena caval occlusions. Both during the control situation and after left circumflex coronary artery occlusion, the calculated and measured stroke volumes were related by a single linear relation ($r = 0.96$, SEE = 1.1 ml).

Statistical methods. Comparisons before and after ischemia were made using a paired *t* test (17). The effect of ischemia on the end-systolic pressure-volume relation in each animal was assessed by analysis of variance of the regression equations (18). All results are summarized as the mean value ± 1 standard deviation, and the level of significance is taken as $p < 0.05$.

Table 1. Hemodynamic Data Before (control) and After (ischemia) Left Circumflex Coronary Artery Occlusion

	Control	Ischemia	p Value
Heart rate (min $^{-1}$)	138 ± 30	137 ± 20	NS
Max dP/dt (mm Hg/s)	2,331 ± 499	2,004 ± 439	< 0.01
Min dP/dt (mm Hg/s)	−2,062 ± 400	−1,640 ± 610	< 0.01
LVEDV (ml)	40.1 ± 14.2	48.5 ± 18.4	< 0.01
LVESV (ml)	28.2 ± 12.5	36.9 ± 16.7	< 0.01
LVEDP (mm Hg)	3.3 ± 1.4	9.3 ± 3.2	< 0.01
LVESP (mm Hg)	110 ± 21	92 ± 22	< 0.01

dP/dt = first derivative of left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; LVESP = left ventricular end-systolic pressure; LVESV = left ventricular end-systolic volume; Max = maximal; Min = minimal.

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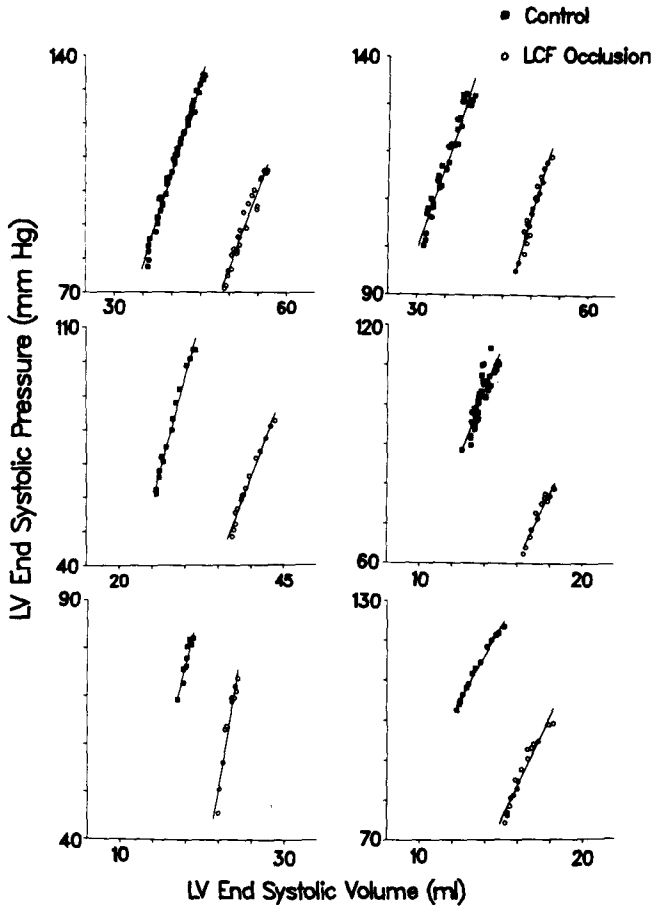

Figure 3. Dogs 1 to 6. The left ventricular (LV) end-systolic pressure-volume relations before and after left circumflex coronary artery (LCF) occlusion. In each animal, regional ischemia shifted the relation to the right.

Results

The hemodynamic data before and after left circumflex coronary artery occlusion are displayed in Table 1. Because of the autonomic blockade, the heart rates were similar before and after the coronary occlusion. In each dog, coronary occlusion produced a decrease in the end-systolic left ventricular pressure and in the maximal and minimal first derivatives of left ventricular pressure (dP/dt). In addition, after coronary occlusion there was an increase in the left ventricular end-systolic and end-diastolic volumes and end-diastolic pressure. The systolic shortening of the septal to lateral left ventricular dimension decreased from 15.3 ± 6.6 to 10.2 ± 5.8%, while the shortening of the antero-posterior dimension (15.6 ± 5.3 to 14.2 ± 8.6%) and long-axis dimension (8.2 ± 4.1 versus 8.3 ± 3.6%) were relatively unchanged. These changes document the production of ischemia by the coronary artery occluder.

End-systolic pressure-volume data. The end-systolic pressure-volume relations from Dogs 1 to 6 are shown in Figure 3. The end-systolic pressure-volume relations in Dog 7 before and after left anterior descending coronary artery occlusion, proximal left circumflex coronary artery occlusion and occlusion of both the proximal left circumflex and distal anterior descending coronary arteries are shown in Figure 4. In each of the seven animals, occlusion of the left circumflex coronary artery shifted the end-systolic pressure-volume relation to the right. In each dog, this shift was highly significant ($p < 0.0001$) by analysis of variance of the regression lines (18). The regression information from each animal is presented in Table 2. In each instance, the end-systolic pressure-volume relation was well described by

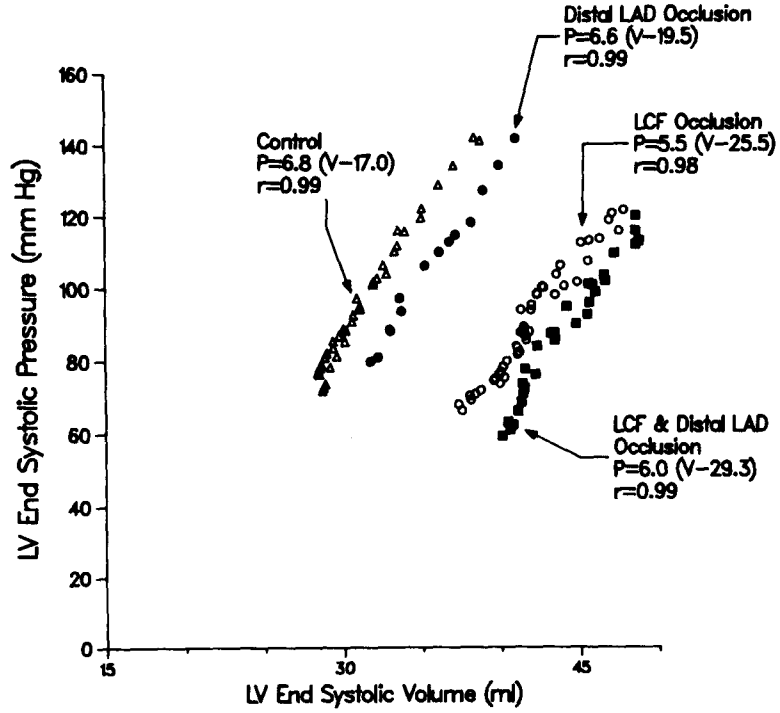

Figure 4. Dog 7. Left ventricular (LV) end-systolic pressure-volume (P-V) relations during the control period and after occlusion of the distal left anterior descending coronary artery (LAD), the proximal left circumflex coronary artery (LCF) and both the distal left anterior descending coronary artery and proximal left circumflex coronary artery. The regression equations for each are shown. Progressively larger amounts of regional ischemia produce greater shifts of the end-systolic pressure-volume relations.

Table 2. Left Ventricular End-Systolic Pressure-Volume Relations Before (control) and After (ischemia) Left Circumflex Coronary Artery Occlusion

Dog	N	r	E (mm Hg/ml)	V_0 (ml)	N	r	E (mm Hg/ml)	V_0 (ml)
1	33	0.975	3.7	3.1	22	0.970	4.2	24.7
2	43	0.983	10.7	4.2	15	0.972	8.9	9.2
3	50	0.994	5.4	20.5	23	0.975	4.5	32.9
4	15	0.992	7.1	16.6	15	0.990	5.1	27.1
5	16	0.995	7.4	1.8	17	0.968	8.7	6.4
6	9	0.950	7.2	7.2	11	0.957	10.6	17.2
7	37	0.991	6.8	17.1	47	0.975	5.2	25.5
Mean ± SD			6.9 ± 2.1	10.1 ± 7.8			6.7 ± 2.6	20.4 ± 9.8*

*$p < 0.005$ compared with control. E = the slope; N = number of points. V_0 = the volume intercept of the left ventricular end-systolic pressure-volume relation.

a linear relation ($r \geq 0.95$). The production of regional ischemia caused an increase in the volume intercept in each animal. The group mean of the volume intercept increased from the control value of 10.1 ± 7.8 to 20.4 ± 9.8 ml ($p < 0.005$) after the production of regional ischemia produced by left circumflex coronary artery occlusion. There was no change in the group mean value (6.9 ± 2.1 versus 6.7 ± 2.6 mm Hg/ml, p = NS) for the slope of the end-systolic pressure-volume relation. The production of progressively larger amounts of regional ischemia in Dog 7 produced greater shifts of the left ventricular end-systolic pressure-volume relation (Fig. 4).

Discussion

Global changes in contractility influence the slope of the left ventricular end-systolic pressure-volume relation without altering the volume intercept of the relation (1–5,8–11). Our study demonstrates that regional left ventricular dysfunction produced by left circumflex coronary artery occlusion in intact ejecting hearts produces a parallel rightward shift of the left ventricular end-systolic pressure-volume relation, increasing the volume intercept while not systematically altering the slope of the relation. Although the linear end-systolic pressure-volume relation was originally described in uniformly contracting ventricles (1–11), the relation remained linear after the production of regional ischemia. The rightward shift of the end-systolic pressure-volume relation during ischemia means that for any given end-diastolic volume and end-systolic pressure, the stroke volume will be reduced. Our findings in intact ejecting hearts are consistent with the recent observations of Sunagawa et al. (12) in isolated, isovolumically beating hearts.

Left ventricular volume calculation. In this study, we determined left ventricular end-systolic volume from three ultrasonically measured left ventricular dimensions. Since regional ischemia alters the end-systolic configuration of the left ventricle, it might affect the validity of our volume calculations. We previously observed (5,14) that our method of left ventricular volume measurement gives consistent results, despite alterations in left ventricular configuration produced by inferior vena cava or pulmonary artery occlusions, volume loading or vasoconstriction. Furthermore, we found that the relation between the stroke volume calculated from the ultrasonically determined left ventricular volume was linearly related to the stroke volume measured by ascending aortic flow probe, both during the control period and after left circumflex coronary artery occlusion. This suggests that the shift of the left ventricular end-systolic pressure-volume relation which we observed during regional ischemia was not due to a systematic alteration of the relation between the actual and calculated left ventricular volume.

Clinical applicability. Several factors should be considered when applying our results to clinical situations. This study was performed after autonomic blockade and sedation to prevent the potentially confounding influences of reflex changes in contractility, heart rate and respiration. In addition, the pericardium was widely opened to allow instrumentation of the animals. Despite these potential limitations, the recent clinical observation of McKay et al. (19) are in agreement with our results. In two patients, they observed that the left ventricular end-systolic volume increased during pacing-induced angina while end-systolic pressure remained nearly constant. This is consistent with a rightward shift of the end-systolic pressure-volume relation during regional ischemia. Our study does not allow assessment of the relative sensitivity of the end-systolic pressure-volume relation and more conventional measurements in detecting regional ischemia, but does suggest, in agreement with Sunagawa et al. (12), that the magnitude of the shift of this pressure-volume relation is related to the amount of regional ischemia.

Mechanism. Changes in contractility, such as those produced by global ischemia, alter the end-systolic stiffness (elastance) of the left ventricle, thus changing the slope of the left ventricular end-systolic pressure-volume relation without shifting the volume intercept (1–11). Why does regional ischemia produce a parallel shift of the end-systolic pressure-volume relation? A model has been proposed in

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which the ventricle is composed of two compartments: a normally functioning portion and an ischemic nonfunctioning component (12,20). The left ventricular end-systolic pressure-volume relation can then be considered as the sum of the relations of the two compartments (12). The nonfunctioning, acutely ischemic region of the left ventricle is thought to continue to operate on a passive pressure-volume relation throughout the cardiac cycle. During systole, the nonischemic portion of the ventricle displaces volume into the ischemic compartment. Because of the exponential nature of the diastolic pressure-volume relation, this increased volume shifts the ischemic compartment up along its pressure-volume relation to a steep portion of the curve, where the slope (or elastance) is similar to the normal systolic value. Thus, the end-systolic pressure-volume relation of the total ventricle has a slope that is close to normal; however, the volume intercept is increased by the volume that has been displaced into the ischemic segment (12). Our results are consistent with this model. The effect of nonischemic causes of regional end-systolic left ventricular dysfunction, such as dyssynchronous electrical activation of the left ventricle (21,22), has not been investigated, but might be expected to produce a similar shift of the end-systolic pressure-volume relation.

Bogen et al. (23) proposed a more complex model of the regionally ischemic ventricle, in which the function of the nonischemic border zone is decreased. This analysis suggests that acute regional ischemia should produce both a rightward shift and a decrease in the slope of the end-systolic pressure-volume relation. Our results do not support this prediction.

Conclusion. This study in ejecting hearts in intact dogs and the previous study of Sunagawa et al. (12) in isolated nonejecting hearts suggest that shifts of the position of the left ventricular end-systolic pressure-volume relation may be a more sensitive indicator of regional left ventricular dysfunction than are changes in the slope of the relation. This finding emphasizes the importance of both the slope and the volume intercept of the end-systolic pressure-volume relation as descriptors of left ventricular function.

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